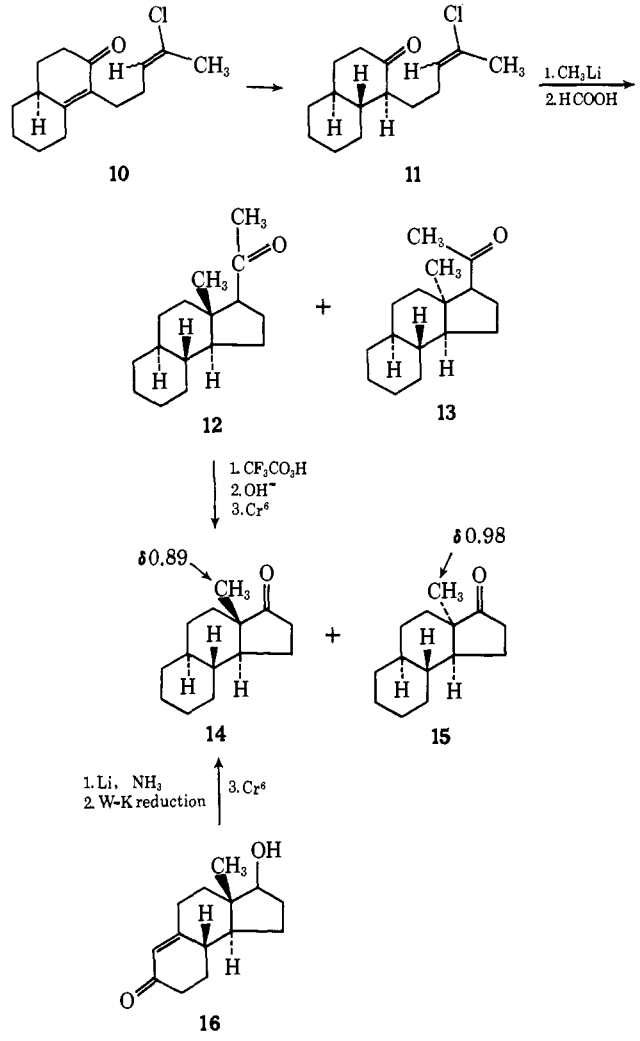
conventional Birch reduction resulted in reduction of the vinyl chloride as well as the enone. Conversion

Scheme II



of **11** to the carbinol with methyllithium proceeded in 85% yield; subsequent formolysis produced a 2:1 mixture of tricyclic ketones[4a] **12** and **13** (*ca.* 90%, based on the carbinol; see Scheme II). Degradation of this mixture[10] gave trans-fused **14**[4a] and its cis epimer **15** in a ratio of *ca.* 65:35 (vpc on SE-30 column, 190°). Presumably this observed ratio closely reflects the relative amounts of **12** and **13** present before the degradation sequence.[10] Both **14** and **15** showed infrared carbonyl bands at 5.75 μ (neat) and the expected M^+ at *m/e* 206. Full confirmation of the stereostructure of **14** was obtained by an alternate, three-step conversion of tricyclic ketone **16**[16] which produced material identical with that from **12**.

It is now clear that the D ring in 20-keto-steroid synthesis can be successfully trans fused onto ABC or BC precursors without subsequent epimerization, when the chloro-olefin side chain, which can be modified in useful ways, is kept equatorial. In closing, we wish to emphasize that these results, taken with earlier ones,[1] broaden the options available for direct construction of functionalized five-membered rings.

(16) Kindly furnished by Dr. G. Nomine of Roussel-Uclaf.

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Nuclear Magnetic Resonance Studies of Poly-DL-alanine and Poly-L-alanine in Solvents with Strong Acids

Sir:

Many polypeptides undergo conformational transitions when solvent composition, or temperature, is varied.[1] In mixed solvents containing strong organic acids, the driving force for the transition may arise from preferential interactions of the peptide residues with the hydrogen-bonding solvent,[2a-c] or from electrostatic repulsions developed from protonation of the amide groups by the strong acid.[3,4]

Many physicochemical techniques have been used to obtain some insight into the molecular basis of these transitions in acid solvents.[4] In recent years nmr investigations have been particularly prevalent.[5] Of

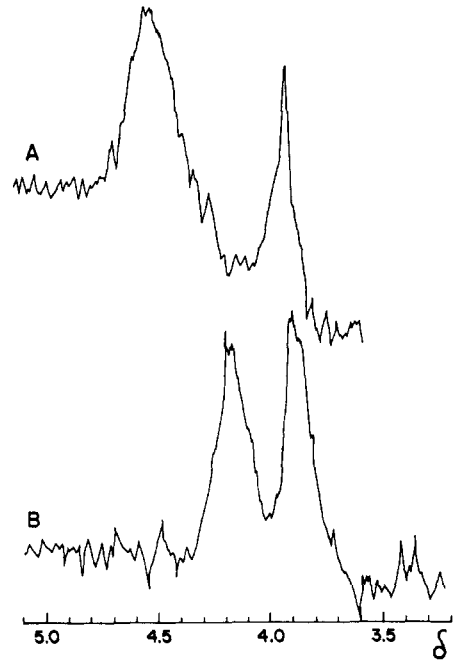

Figure 1. Nuclear magnetic resonance spectra of: A, 0.1% poly-DL-alanine in 12% CF_3COOH–88% $CDCl_3$; B, 0.1% poly-L-alanine in 1% CF_3COOH–99% $CDCl_3$. Chemical shift, δ, in parts per million, downfield from tetramethylsilane reference.

(1) G. D. Fasman, Ed., "Poly-α-amino Acids," Marcel Dekker, New York, N. Y., 1967, and references cited therein.
(2) (a) W. E. Stewart, L. Mandelkern, and R. E. Glick, *Biochemistry*, **6**, 143 (1967); (b) F. A. Bovey, *Pure Appl. Chem.*, **16**, 417 (1968); (c) J. A. Ferretti and B. W. Ninham, *Macromolecules*, **3**, 30 (1970), and references cited therein.
(3) S. Hanlon and I. M. Klotz, *Biochemistry*, **4**, 37 (1965).
(4) J. H. Bradbury and M. D. Fenn, *Aust. J. Chem.*, **22**, 357 (1969), and references cited therein.
(5) G. C. K. Roberts and O. Jardetzky, *Advan. Protein Chem.*, **24**, 447 (1970).

Table I. Chemical Shifts and Line Widths of α-CH Proton of Polyalanines in CF_3COOH–$CDCl_3$ Mixtures

Polymer	% CF_3COOH	δ_h[a]	W_h[b]	δ_l[a]	W_l[b]	Area (l)[c] / Area (h)
Poly-L-alanine	0	3.72	21			0
	1	3.87	15	4.16	16	1
	100			4.68	17	∞
Poly-DL-alanine	0	3.72	20			0
	1	3.90	17	4.26	26	1.85
	3	3.91	16	4.32	28	2.10
	5	3.92	15	4.39	27	2.60
	8	3.92	16	4.47	26	2.96
	12	3.91	14	4.51	21	3.20
	100			4.72	18	∞

[a] Chemical shifts (parts per million) downfield from internal tetramethylsilane standard. δ_h refers to high-field peak, δ_l to low-field peak. [b] Line widths in hertz; W_h refers to high-field peak, W_l to low-field peak. [c] Relative areas of peaks.

Table II. Chemical Shifts for α-CH Proton in Polypeptides

Polymer	Solvent	δ (ppm) for conformation assigned from optical rotatory dispersion: Helix	Random
Poly-γ-benzyl-L-Glu[a,b]	$CDCl_3$	3.95	
Poly-γ-benzyl-DL-Glu[c]	$CDCl_3$		3.95
Poly-γ-benzyl-L-Glu[c]	$DCON(CD_3)_2$	4.10	
Poly-γ-benzyl-DL-Glu[c]	$DCON(CD_3)_2$		4.25
Poly-γ-benzyl-L-Glu[b,d]	$CDCl_3$–CF_3COOH	3.95	4.55
Poly-γ-benzyl-DL-Glu[a]	$CDCl_3$–CF_3COOH		4.45
Poly-γ-benzyl-L-Glu[e]	$CDCl_3$–$CHCl_2COOH$	3.98	4.53
Poly-β-benzyl-L-Asp[c]	$CDCl_3$–CF_3COOH	4.28	4.65
Poly-β-methyl-DL-Asp[c]	$CDCl_3$		4.41
Poly-β-methyl-DL-Asp[c]	$CDCl_2$–CF_3COOH		4.81
Copoly-L-Glu^{42}-L-Lys^{28}-L-Ala^{30} [f]	D_2O (pD = 2.5)	4.22[g]	4.22[g]

[a] E. M. Bradbury, C. Crane-Robinson, H. Goldman, and H. W. E. Rattle, *Nature (London)*, **217**, 812 (1968). [b] Data were also obtained in this laboratory and are identical. [c] E. M. Bradbury, B. G. Carpenter, C. Crane-Robinson, and H. W. E. Rattle, *Nature (London)*, **220**, 69 (1968). [d] J. A. Ferretti and B. W. Ninham, *Macromolecules*, **3**, 30 (1970). [e] J. H. Bradbury and M. D. Fenn, *Aust. J. Chem.*, **22**, 357 (1969). [f] E. M. Bradbury, C. Crane-Robinson, H. Goldman, and H. W. E. Rattle, *Biopolymers*, 6, 851 (1968). [g] This chemical shift was determined with respect to the water-soluble reference compound, sodium 2,2-dimethyl-2-silapentane-5-sulfonate. In all the other solvents tetramethylsilane provided the reference peak.

special interest from such studies has been the observation of two different resonances from the α-CH of the peptide residue which generally have been assigned to helical *vs.* random-coil environments.[6]

Since the relative intensities of these two α-CH resonances vary with content of organic acid in the mixed solvent, it is also possible that they respond primarily to the extent of protonation of the amide groups, rather than to the conformation of the polymer. One way to discriminate between these alternatives is to compare the behavior of a DL-polypeptide with that of a corresponding configurationally pure L-polypeptide, since in the former, helix formation should be absent or minimal in any solvent.

Poly-DL-alanine (Yeda lot A49, mol wt 1600) and poly-L-alanine (Yeda lot AL41, mol wt 1670) were examined in mixed solvents constituted, in various proportions, from purified trifluoroacetic acid and (99.8% D) deuteriochloroform (with 1% tetramethylsilane for reference marker). All solutions were prepared in a drybox and were examined within a few hours after preparation. Polymer concentrations were 0.1% (w/v) or less. Nmr spectra were recorded on a Bruker 90-MHz spectrometer equipped with a Fabri-Tek Model 1074 computer of average transients. In most experiments an accumulation of 128 scans gave a satisfactory signal-to-noise ratio.

(6) E. M. Bradbury, C. Crane-Robinson, H. Goldman, and H. W. E. Rattle, *Nature (London)*, **217**, 812 (1968).

Dissolved in $CDCl_3$, poly-DL-alanine shows a single resonance peak (δ 3.72 ppm) for the α-CH proton (see Table I). Upon addition of CF_3COOH, even as little as 1%, the original peak is shifted slightly (δ 3.90 ppm), and a new resonance peak appears (Figure 1) about 0.4 ppm downfield (δ 4.26 ppm). The relative area of this new peak increases with increasing concentration of CF_3COOH[7] (Table I) whereas that of the high-field 3.9-ppm resonance decreases. In CF_3COOH solutions the chemical shift of the high-field resonance peak as well as its line width are independent of acid concentration. In contrast the resonance frequency of the low-field peak shifts progressively downfield with increasing acid concentration (Table I). In acid solutions the line width of the low-field peak is always greater than that of the high-field resonance.

Poly-L-alanine behaves very much like poly-DL-alanine (Table I). In pure $CDCl_3$ the L-polymer shows a single peak at δ 3.72 ppm. Addition of 1% CF_3COOH generates a new resonance at δ 4.16 ppm. This is shifted further downfield in pure CF_3COOH. The relative area of the low-field peak is less in the L-polymer than in the DL-polypeptide in solutions of the same acid concentration.

On the basis of enzymic digestion studies, Linderstrøm-Lang[8] concluded that the distribution of D and

(7) Since the acid solutions might be hydrolyzing the polypeptide, a second series of scans was accumulated (for some solutions) several hours after the first series. The relative areas of the resonance peaks were essentially unchanged. Clearly no significant hydrolysis occurred.

L residues in poly-DL-alanine is very nearly random. Furthermore, Englander and Poulsen[9] have shown that hydrogen–tritium exchange rates of poly-DL-alanine (degree of polymerization = 29) are similar to those of random chain polypeptides and unhindered amide nitrogens. It seems reasonable to assume, therefore, that the DL-polymer used in the present studies is in a random coil, disordered conformation throughout the entire range of solvent compositions. Consequently, the resonance at 3.72 ppm in the DL-polymer in $CDCl_3$ and 3.9 ppm in $CDCl_3$–CF_3COOH mixtures cannot be an expression of a helical conformation. Furthermore, the simultaneous presence of two resonances in solvent mixtures containing acid cannot be ascribed to the simultaneous presence of two conformations, helical and random coil macromolecules in solution. These shifts, however, are thoroughly consistent with the view that addition of CF_3COOH to the polypeptide solution leads to protonation of the amide group.

Values of the chemical shifts of the α-CH proton of other synthetic polypeptides in various solvents are assembled in Table II. The δ observed is placed in the "helix" or "random" column on the basis of the diagnosis of conformation provided by optical rotatory dispersion measurements. For polybenzyl-DL-glutamate Tsuboi, *et al.*,[10] found that 70% of the residues are in the random conformation in the polypeptide with a degree of polymerization of about 80. Nevertheless, dissolved in $CDCl_3$, the disordered DL-polymer shows the same δ (3.95 ppm) as does the helical L-polymer.[11] Likewise, both show a shift in δ to 4.45 ppm in the mixed solvent CF_3COOH–$CDCl_3$.

We conclude, therefore, that the previous assignment of the α-CH nmr resonances to helical and random conformations is not tenable since DL- and L-polymers show essentially the same δ's. Similarly the attribution of low-field and high-field α-CH peaks to different molecular weight fractions of a polydisperse sample of polypeptide is also not likely since in essence this explanation also depends on the assignment of different δ's to helical *vs.* coil conformations.[5,12] On the other hand, the parallel behavior of DL- and L-polymer, particularly in the detailed study of polyalanine, is consistent with the interpretation of the effect of added strong organic acids as due to protonation of the amide groups.[3,4,13]

Acknowledgment. This investigation was supported in part by a research grant (No. GM-09280) from the National Institute of General Medical Sciences, U. S. Public Health Service.

(8) K. Linderstrøm-Lang, *Acta Scand.*, **12**, 851 (1958).
(9) S. W. Englander and A. Poulsen, *Biopolymers*, **7**, 379 (1969).
(10) M. Tsuboi, Y. Mitsui, A. Wada, T. Miyazawa, and N. Nagashima, *ibid.*, **1**, 297 (1963).
(11) E. M. Bradbury, B. G. Carpenter, C. Crane-Robinson, and H. W. E. Rattle, *Nature (London)*, **220**, 69 (1968).
(12) R. Ullman, *Biopolymers*, **9**, 471 (1970).
(13) This implies that the protonation step should be slow (on an nmr time scale). A similar conclusion has been reached previously by J. H. Bradbury, M. D. Fenn, and A. G. Moritz, *Aust. J. Chem.*, **22**, 2443 (1969), and is also implicit in the studies of W. E. Stewart, L. Mandelkern, and R. E. Glick, *Biochemistry*, **6**, 150 (1967).

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Book Reviews

The Mathematical Theory of Non-Uniform Gases. An Account of the Kinetic Theory of Viscosity. Thermal Conductivity and Diffusion in Gases. Third Edition. By SYDNEY CHAPMAN, F.R.S., Geophysical Institute, College, Alaska, National Center for Atmospheric Research, Boulder, Colo., and T. G. COWLING, F.R.S., Professor of Applied Mathematics, Leeds University. Cambridge University Press, 32 East 57th St., New York, N. Y. 1970. xxiv + 423 pp. 16 × 23.5 cm. $16.00.

This third edition of the "Mathematical Theory of Non-Uniform Gases," although extensively revised, continues in the same spirit as the two previous editions. As the authors state, the book is addressed to the mathematician and theoretical physicist but with an effort, which is by and large successful, to gather the results together in such a way as to be useful to experimentalists in physics and chemistry. The methods used are those of statistical mechanics so that an equally descriptive title would have been the Statistical Mechanics of Non-Uniform Gases except that it would have left out the bias toward analytical solutions. Thus the authors make no mention of the extensive numerical calculations now being made of the mechanical behavior of around a thousand interacting molecules. Such results are especially useful in checking analytical solutions of proposed models. However, the qualified readers will find here a clear, concise, self-contained theory of not too dense gases.

Classical mechanics is used in general, but quantum mechanical corrections are introduced where needed, and quantum theory is applied to transport properties in a direct workmanlike way in Chapter 17. The final chapter on electromagnetic phenomena in ionized gases is especially interesting and is in keeping with the high standards of the rest of the book. A final historical summary highlighting major developments in the theory of gases closes with Chapman and Enskog's development of the complete equations of diffusion on heat conduction in a mixed gas. The history after 1920 must be gleaned from the rest of the book. Anyone interested in the theory of gases cannot afford to be unacquainted with this book.

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The Chemical Physics of Ice. By N. H. FLETCHER, Professor of Physics, University of New England, Armidale, New South Wales. Cambridge University Press, 32 East 57th St., New York, N. Y. 1970. x + 271 pp. 15 × 22 cm. $13.50.

In his preface Dr. Fletcher states that he has written the book for senior undergraduate and graduate students in physics or physical chemistry, and for scientists interested in ice for its own sake—glaciologists, cloud physicists, and the like. He further states that he has not tried to be encyclopaedic but has tried to produce a connected and well-documented account of what seems to him to be the major areas of interest. The reviewer's main thoughts are that he has succeeded magnificently in his objectives, that the book